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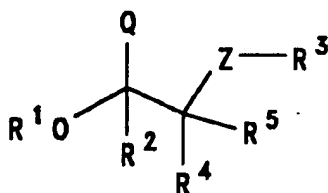
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| <p>(21) International Application Number: PCT/GB93/01863</p> <p>(22) International Filing Date: 3 September 1993 (03.09.93)</p> <p>(30) Priority data:</p> <table><tr><td>9219175.8</td><td>10 September 1992 (10.09.92)</td><td>GB</td></tr><tr><td>9223793.2</td><td>13 November 1992 (13.11.92)</td><td>GB</td></tr></table> <p>(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only) : HUSCROFT, Ian, Thomas [GB/GB]; 27 Elm Road, Bishops Stortford, Hertfordshire CM23 2SS (GB). STEVENSON, Graeme, Irvine [GB/GB]; Ridgemean, Thaxted Road, Debden, Saffron Walden, Essex CB11 3LW (GB). WILLIAMS, Brian, John [GB/GB]; 73 Godfrey Way, Great Dunmow, Essex CM6 2SE (GB).</p> | 9219175.8 | 10 September 1992 (10.09.92) | GB | 9223793.2 | 13 November 1992 (13.11.92) | GB | <p>(74) Agent: QUILLIN, Helen, Kaye; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p> |
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(54) Title: ALCOHOLS AND ETHERS WITH AROMATIC SUBSTITUENTS AS TACHYKININ-ANTAGONISTS



(I)

(57) Abstract

Compounds of formula (I), and salt and prodrugs thereof, wherein Q is optionally substituted phenyl or benzhydryl; R¹ is H; optionally substituted C₁₋₆alkyl; optionally substituted phenyl(C₁₋₄alkyl); C₂₋₆alkenyl; C₂₋₆alkynyl; COR^a; COOR^a; COHet; COC₁₋₆alkylhalo; COC₁₋₆alkylNR^aR^b; CONR¹²C₁₋₆alkylCONR^aR^b; CONR^aR^b; or SO₂R^a; R² represents H, C₁₋₆alkyl or C₂₋₆alkenyl; or R¹ and R² together form a chain (CH₂)_q optionally substituted by oxo where q is 4 or 5 and where one methylene group may optionally be replaced by an oxygen atom or a group NR^x, where R^x is H or C₁₋₆alkyl; R³ is C₁₋₃alkyl substituted by optionally substituted phenyl; R⁴ and R⁵ are each H, C₁₋₆alkyl or C₂₋₆alkenyl; and Z represents O or S; are tachykinin receptor antagonists useful in therapy.

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ALCOHOLS AND ETHERS WITH AROMATIC SUBSTITUENTS AS TACHYKININ-ANTAGONISTS

5 This invention relates to a class of
azabicyclic compounds, which are useful as tachykinin
antagonists. More particularly, the compounds of the
invention comprise an aromatic moiety and an hydroxy or
alkoxy moiety.

10 The tachykinins are a group of naturally-
occurring peptides found widely distributed throughout
mammalian tissues, both within the central nervous system
and in the peripheral nervous and circulatory systems.
The three known mammalian tachykinins are:
substance P, neurokinin A and neurokinin B:

15 Evidence for the usefulness of tachykinin
receptor antagonists in pain, headache, especially
migraine, Alzheimer's disease, multiple sclerosis,
attenuation of morphine withdrawal, cardiovascular
changes, oedema, such as oedema caused by thermal injury,
20 chronic inflammatory diseases such as rheumatoid
arthritis, asthma/bronchial hyperreactivity and other
respiratory diseases including allergic rhinitis,
inflammatory diseases of the gut including ulcerative
colitis and Crohn disease, ocular injury and ocular
25 inflammatory diseases, proliferative vitreoretinopathy,
irritable bowel syndrome and disorders of bladder
function including cystitis and bladder detrusor hyper-
reflexia is reviewed in "Tachykinin Receptors and
Tachykinin Receptor Antagonists", C.A. Maggi, R.
30 Patacchini, P. Rovero and A. Giachetti, J. Auton.
Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are
also believed to be useful in allergic conditions
[Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66
1361-7], immunoregulation [Lotz et al Science (1988) 241

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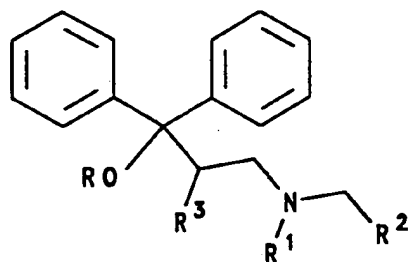
1218-21 and Kimball et al., J. Immunol. (1988) 141 (10) 3564-9], and as anticonvulsants [Garant et al., Brain Research (1986) 382 372-8]. Tachykinin antagonists may also be useful in the treatment of small cell carcinomas,
5 in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive
10 airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis, reflex sympathetic dystrophy such as shoulder/hand syndrome,
15 addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythematosis (European patent application no. 0 436 334), conjunctivitis, vernal conjunctivitis,
20 contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

We have now found a class of non-peptides which
25 are potent antagonists of tachykinins.

GB1377350 discloses compounds of formula (A):

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(A)

10 wherein:

R is C₁₋₄alkyl;

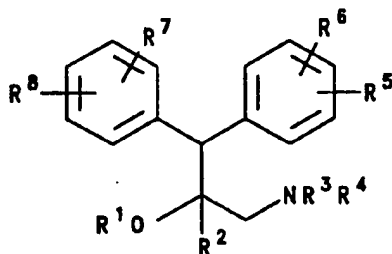
R¹ is H, C₁₋₄alkyl, alkyl or benzyl;

R² is inter alia aralkenyl; and

R³ is H or methyl.

15 The compounds are said to have analgesic and morphine-antagonistic actions.

GB 1443441 and GB 1448437 discloses compounds of formula (B):



(B)

wherein:

30 R¹ is H, R⁹ or COR⁹, where R⁹ is phenyl, benzyl or C₁₋₆alkyl optionally substituted by NR¹⁰R¹¹;

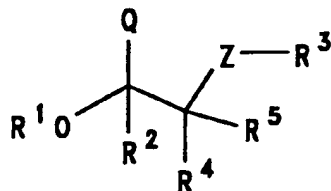
R² and R⁴ are each H, methyl or ethyl; and

R³ is H, methyl, ethyl or benzyl.

The compounds are said to be useful in the treatment of depression.

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The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

Q represents optionally substituted phenyl or optionally substituted benzhydryl;

R¹ represents: H;

15 C₁-6alkyl optionally substituted by hydroxy, cyano, COR^a, COOR^a, CONR^aR^b, COC₁₋₆alkylNR^aR^b, CONR¹²C₁₋₆alkylOR^a; Het; COHet; CONR¹²C₁₋₆alkylHet; CONR¹²C₁₋₆alkylCONR^aR^b or NR^aR^b;

20 phenyl(C₁₋₄alkyl) (optionally substituted by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl in the phenyl ring);

C₂-6alkenyl;

C₂-6alkynyl;

COR^a;

25 COOR^a;

COHet;

COC₁₋₆alkylhalo;

COC₁₋₆alkylNR^aR^b;

CONR¹²C₁₋₆alkylCONR^aR^b;

30 CONR^aR^b; or

SO₂R^a;

R² represents H, C₁-6alkyl or C₂-6alkenyl;

or R¹ and R² together form a chain (CH₂)_q optionally substituted by oxo where q is 4 or 5 and where

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one methylene group may optionally be replaced by an oxygen atom or a group NR^x , where R^x is H or C_{1-6} alkyl;

R^3 represents C_{1-3} alkyl substituted by a phenyl group which may itself optionally be substituted by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^c , SOR^c , SO_2R^c , OR^c , NR^cR^d , NR^cCOR^d , NR^cCOOR^d , COOR^c and CONR^cR^d ;

R^4 and R^5 each represent H, C_{1-6} alkyl or C_{2-6} alkenyl;

Z represents O or S;

R^{12} represents H, C_{1-6} alkyl, phenyl (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl) or phenyl(C_{1-4} alkyl) (optionally substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl);

R^a and R^b each independently represent H, C_{1-6} alkyl, phenyl (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl), phenyl(C_{1-4} alkyl) (optionally substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl) or R^a and R^b together form a chain $(\text{CH}_2)_p$ optionally substituted by oxo where p is 4 or 5 and where one methylene group may optionally be replaced by an oxygen atom or a group NR^x , where R^x is H or C_{1-6} alkyl;

R^c and R^d independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl; and

Het represents an aromatic heterocycle optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, oxo, thioxo, halo, trifluoromethyl, NR^aR^b , NR^aCOR^b , CONR^aR^b , CO_2R^a , SR^a , SO_2R^a or CH_2OR^a , where R^a and R^b are as above defined.

As used herein, the definition of each expression, when it occurs more than once in any

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structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the formulae herein may
5 represent straight, branched or cyclic groups or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as
10 cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

For phenylalkyl substituents, the alkyl moiety may be straight or branched.

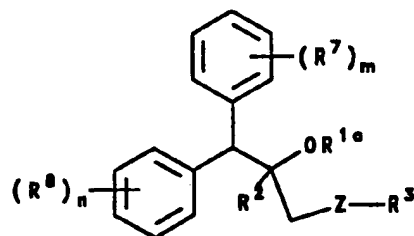
The term "halo" as used herein includes fluoro,
15 chloro, bromo and iodo.

Where Q represents substituted phenyl or benzhydryl, suitable substituents include C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO₂R^a, OR^a,
20 NR^aR^b, NR^aCOR^b, NR^aCOOR^b, COOR^a or CONR^aR^b, where R^a and R^b are as above defined. One or more substituents may be present and each may be located at any available ring position.

Suitably Het represents an optionally
25 substituted heteroaryl moiety selected from thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, triazinyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl,
30 imidazolyl, benzimidazolyl, benzoxazolyl, benzothienophenyl, benzofuranyl and indolyl.

A subgroup of compounds of the present invention is represented by compound of formula (IA), and salts and prodrugs thereof:

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(IA)

10 wherein

Z , R^2 and R^3 are as defined for formula (I) above;

R^{1a} represents H or C_{1-6} alkyl optionally substituted by hydroxy, cyano, COR^a , $COOR^a$, $CONR^aR^b$,
 15 $COC_{1-6}alkylNR^aR^b$, $CONR^{12}C_{1-6}alkylOR^a$,
 $CONR^{12}C_{1-6}alkylCONR^aR^b$ or NR^aR^b (where R^a , R^b and R^{12} are as defined for formula (I) above); phenyl(C_{1-4} alkyl) (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl in the phenyl ring);
 20 C_{2-6} alkenyl; C_{2-6} alkynyl; COR^a ; $COOR^a$; $COC_{1-6}alkylhalo$; $COC_{1-6}alkylNR^aR^b$; $CONR^{12}C_{1-6}alkylCONR^aR^b$; $CONR^aR^b$; or SO_2R^a ; or R^1 and R^2 together form a chain $(CH_2)_q$ optionally substituted by oxo where q is 4 or 5 and where one methylene group may optionally be replaced by an
 25 oxygen atom or a group NR^x , where R^x is H or C_{1-6} alkyl;

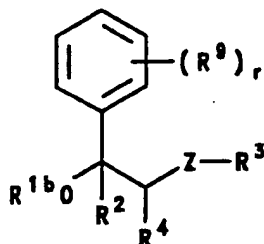
each R^7 independently represents C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl;

each R^8 independently represents C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl; and

30 n and m each represent 0, 1, 2 or 3.

A second subgroup of compounds of the present invention is represented by compounds of formula (IB), and salts and produgs thereof:

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(18)

10 wherein Z , R^3 and R^4 are as defined for formula (I) above;

R^{1b} represents: H;

C_{1-6} alkyl optionally substituted by hydroxy, cyano, COR^a , $COOR^a$, $CONR^aR^b$, $COC_{1-6}alkylNR^aR^b$,
 15 $CONR^{12}C_{1-6}alkylOR^a$, Het; COHet; $CONR^{12}C_{1-6}alkylCONR^aR^b$ or NR^aR^b ;

phenyl(C_{1-4} alkyl) (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl in the phenyl ring);

20 C_{2-6} alkenyl;

C_{2-6} alkynyl;

COR^a ;

$COOR^a$;

COHet;

25 $COC_{1-6}alkylhalo$;

$COC_{1-6}alkylNR^aR^b$;

$CONR^{12}C_{1-6}alkylCONR^aR^b$;

$CONR^aR^b$; or

SO_2R^a ;

30 where R^a , R^b and R^{12} are as defined for formula (I) above;

R^2 represents H, C_{1-6} alkyl or C_{2-6} alkenyl;

each R^9 independently represents C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl;

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r represents 0, 1, 2 or 3; and

Het represents an aromatic heterocycle

optionally substituted by C₁-6alkyl, C₁-6alkoxy, oxo, thioxo, halo, trifluoromethyl, NR^aR^b, NR^aCOR^b, CONR^aR^b,
5 CO₂R^a, SR^a, SO₂R^a or CH₂OR^a, where R^a and R^b are as above defined.

One subgroup of compounds according to the invention is represented by compounds of formula (I) wherein Q is optionally substituted benzhydryl.

10 A further subgroup of compounds according to the invention is represented by compounds of formula (I) wherein Q is optionally substituted phenyl.

In the compounds of formula (I) it is preferred that Q is unsubstituted phenyl or unsubstituted
15 benzhydryl.

Preferably R¹ represents H or substituted C₁-6alkyl, more preferably CH₂ substituted by a group CONR^aR^b, such as CONH₂, COOR^a, such as COOCH₃, or
20 CONR¹²C₁-6alkylHet, such as CONR¹²CH₂Het, in particular CONR¹²CH₂pyridyl. More preferably R¹ represents CH₂CONR^aR^b or CH₂CONR¹²C₁-6alkylHet. Another suitable value for R¹ is C₁-6alkyl substituted by Het such as optionally substituted triazolyl, thiazolyl, oxadiazolyl or imidazolyl.

25 Suitable values for the groups R², R⁴ and R⁵ include H and methyl, preferably H.

Suitably R³ represents a C₁-3alkyl, such as CH₂CH(CH₃) or C(CH₃)₂, bearing a substituent which is a substituted phenyl group. Suitable phenyl substituents
30 include C₁-6alkyl such as i-butyl, t-butyl, i-propyl, cyclopropyl, ethyl and especially methyl, C₁-6alkoxy such as i-propoxy, ethoxy, and especially methoxy, phenoxy, nitro, cyano, halo such as bromo, chloro, fluoro and iodo, and trifluoromethyl. Preferably R³ represents CH₂

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substituted by a substituted phenyl group. Preferably one or two substituents selected from C₁₋₄alkyl, such as methyl and t-butyl, C₁₋₄alkoxy, such as methoxy, trifluoromethyl and halo such as bromo, chloro, fluoro and iodo will be present in the phenyl ring. More preferably R³ represents CH₂ substituted by 3,5-disubstituted phenyl, such as 3,5-dimethylphenyl or 3,5-bistrifluoromethylphenyl.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily

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convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least one asymmetric centre, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK1R, thereby affording an IC₅₀ value for the test compound. The compounds of the Examples were found to have IC₅₀ values less than 200nM.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition

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comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into
5 association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose,
10 sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-
15 toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally
20 effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or
25 pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope
30 over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers

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or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

5 The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil
10 suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums
15 such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

 Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures
20 thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably
25 sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine.
30 Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

 For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable

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carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other

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neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinoma such as small cell lung cancer;

5 respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, irritable bowel syndrome, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such

10 as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like, and proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and

15 other eczematoid dermatitis; oedema, such as oedema caused by thermal injury; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such

20 as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as

25 ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in intracranial pressure; disorders of bladder

30 function such as cystitis and bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease;

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and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

5 The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis
10 and especially migraine.

 The present invention further provides a compound of formula (I) for use in therapy.

 According to a further or alternative aspect, the present invention provides a compound of formula (I)
15 for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

 The present invention also provides a method for the treatment or prevention of physiological
20 disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

25 For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a
30 compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the

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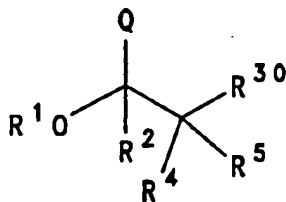
bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

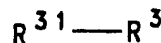
The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds according to the invention may be prepared by reaction of compounds of formula (II) with compounds of formula (III)



(II)



(III)

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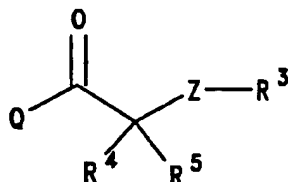
wherein Q, R², R³, R⁴ and R⁵ are as defined for formula (I), R¹ is as defined for formula (I) **except that**, when R¹ is H it is replaced by a suitable protecting group, such as tetrahydropyranyl; and one of R³⁰ and R³¹ represents a leaving group and the other of R³⁰ and R³¹ represents ZH, where Z is as defined for formula (I); in the presence of a base, followed by deprotection, if required.

Suitably R³⁰ represents ZH and R³¹ represents a leaving group.

Suitable leaving groups include halo, e.g. chloro, bromo or iodo, or sulphonate derivatives such as tosylate or mesylate.

The reaction is conveniently carried out in a suitable organic solvent, such as dimethylformamide, at a temperature in the region of 0°C. Favoured bases of use in the reaction include alkali metal hydrides, such as sodium hydride.

Alternatively, compounds of formula (I) wherein R¹ is H and R² is H may be prepared by reduction of compounds of formula (IV):



(IV)

wherein Q, R³, R⁴, R⁵ and Z are as defined for formula (I).

Suitable reducing agents of use in the reaction include hydride reducing agents, such as, for example, sodium borohydride.

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The reaction is conveniently effected in a suitable organic solvent, such as an alcohol, e.g. methanol, suitably at room temperature.

Compounds of formula (I) where R^2 is other than H may be prepared from compounds of formula (II) by reaction with a Grignard reagent of formula R^2MgHal , wherein Hal is as previously defined. Suitable reagents and conditions will be readily apparent to those skilled in the art.

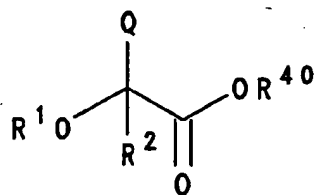
Compounds of formula (I) may also be prepared from different compounds of formula (I) by interconversion processes. In particular, interconversion processes may be used to vary the group R^1 . For example, compounds of formula (I) wherein R^1 is other than H may be prepared from the corresponding compounds of formula (I) wherein R^1 is H by conventional methods, such as reaction with a compound R^1-Hal , where Hal represents halo, in the presence of a base. Suitable reagents and conditions will be readily apparent to those skilled in the art and are illustrated by the accompanying Examples. Suitable bases include organic bases, such as tertiary amines, e.g. triethylamine, and inorganic bases, such as alkali metal carbonates, e.g. sodium carbonate. Compounds of formula (I) wherein R^1 is C_{1-6} alkyl substituted by $CONR^aR^b$ may be prepared from corresponding compounds of formula (I) wherein R^1 is C_{1-6} alkyl substituted by CO_2R^a by treatment with ammonia or an amine of formula NR^aR^b .

The intermediates of formula (II) above wherein R^{30} is SH may be prepared from the corresponding intermediates of formula (II) wherein R^{30} represents OH by treating the latter compound with hydrogen sulphide in the presence of aluminium oxide, as described by Lucien *et al.*, Nouveau J. Chem., 3, 15 (1979), or phosphorus

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pentasulphide in a suitable solvent, e.g. pyridine, at ambient or elevated temperatures, suitably at reflux temperature.

- Intermediates of formula (II) above wherein R³⁰ is OH and R⁴ is H may be prepared from corresponding compounds of formula (V):



(V)

- wherein Q, R¹ and R² are as defined for formula (II) and R⁴⁰ represents alkyl, by reduction.

Suitable reducing agents of use in the reaction include metal hydrides, for example, lithium aluminium hydride. The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran.

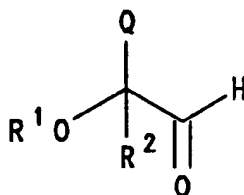
- Compounds of formula (V) wherein R¹ is other than H may be prepared from the corresponding compounds of formula (V) wherein R¹ is H by reaction with a reagent suitable to introduce the group R¹ as defined for formula (II) using conventional procedures. General methods for introducing the group R¹ are discussed above for the preparation of compounds of formula (I). Suitable procedures are described in the Examples and further procedures will be readily apparent to those skilled in the art.

Compounds of formula (V) wherein R¹ is H are commercially available or maybe prepared from commercially available starting materials using

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conventional methods well known to those skilled in the art.

Compounds of formula (II) wherein R^{30} is OH and R^4 and/or R^5 are other than H may be prepared from intermediates of formula (VI)



(VI)

wherein Q , R^1 and R^2 are as defined for formula (II), by reaction with an organometallic reagent of formula MR^4 and/or MR^5 , wherein R^4 and R^5 are as previously defined and M represents a metal, such as lithium, or a metal halide, such as a magnesium halide, e.g. magnesium chloride or magnesium bromide.

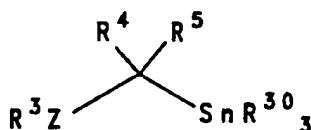
The reaction is suitably effected in an inert organic solvent such as an ether, for example, diethylether or tetrahydrofuran.

Aldehydes of formula (VI) may be prepared by reduction of esters of formula (V) wherein R^{40} is alkyl using diisobutylaluminium hydride.

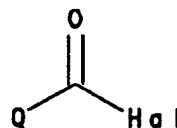
Compounds of formula (IV) may be prepared by reaction of a compound of formula (VII) with a compound of formula (VIII)

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(VII)

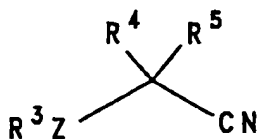


(VIII)

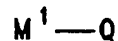
10 wherein Q, R³, R⁴, R⁵, Z and Hal are as previously defined and R³⁰ represents alkyl, such as butyl.

The reaction is preferably effected in the presence of a suitable catalyst, such as palladium (II) catalyst, for example benzylchlorobis(triphenylphosphine) palladium(II), conveniently in a suitable organic
15 solvent, such as a halogenated hydrocarbon, e.g. chloroform, preferably at elevated temperature, such as 60-100°C.

Alternatively, compounds of formula (IV) may be prepared by reaction of a compound of formula (IX) with a
20 compound of formula (X)



(IX)



(X)

30 wherein Q, R³, R⁴, R⁵ and Z are as previously defined and M¹ represents an alkali metal, such as lithium.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. diethyl ether. Preferably the reaction is effected at low temperature, such as about -80°C, and the reaction

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mixture subsequently allowed to reach ambient temperature.

Compounds of formula (VII) may be prepared from the corresponding alcohols of formula R^3OH by reaction
5 with a compound of formula $Hal-CH_2SnR^{30}_3$, wherein R^{30} and Hal are as previously defined, in the presence of a base, such as an alkali metal hydride, e.g. sodium hydride.

Compounds of formulae R^3OH and (VIII) are commercially available or may be prepared from
10 commercially available starting materials by conventional methods.

Compounds of formula $Hal-CH_2SnR^{30}_3$ are commercially available.

Compounds of formula (IX) may be prepared by
15 reaction of halides of formula R^3Hal , wherein R^3 and Hal are as previously defined, with cyanohydrin.

Compounds of formula R^3Hal are commercially available or may be prepared from commercially available starting materials by conventional methods.

20 Intermediates of formula (VI) are conveniently not isolated but generated in situ using a metallating agent, such as a lithiating agent, e.g. n-butyl lithium.

Where the above-described process for the preparation of the compounds according to the invention
25 gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by
30 enantiospecific synthesis or by resolution. For example, compounds of formula (I) wherein R^1 is H may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the

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chiral auxiliary. These compounds can then be used to make individual enantiomers of compounds of formula (I) wherein R^1 is other than H.

During any of the above synthetic sequences it
5 may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973;
10 and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the
15 preparation of compounds according to the invention.

- 25 -

EXAMPLE 11-(3,5-Bis(trifluoromethyl)phenyl)methoxy-3,3-diphenyl-2-hydroxypropane

5 a) Preparation of 1-(3,5-bis(trifluoromethyl)phenyl)
methoxy-3,3 diphenylacetone
Method A

10 i) Sodium hydride (80% suspension in oil, 2.03g) was washed twice with petroleum ether and to this solid was added tetrahydrofuran (50ml) and dimethylformamide (3ml) followed by the slow addition of a solution of 3,5-bis(trifluoromethyl) benzyl alcohol (15g) in tetrahydrofuran (50ml). After the effervescence had subsided (30 minutes) a solution of tri-n-butyltinmethylene iodide (25.2g) was added. The solution
15 was heated to reflux for 2 hours, cooled to room temperature and quenched by careful addition of petroleum ether bp 60-80°C (500ml) and water (200ml). The organic phase was washed with water and dried (MgSO₄). After removal of the solvent in vacuo the residue was distilled under reduced pressure bp_{0.8} = 140°C to
20 give tri-n-butyl-((3,5- bis(trifluoromethyl)phenyl)
methoxymethyl)tin. ¹H NMR (360MHz, CDCl₃) δ 7.78 (1H, s, 4-aryl-H), 7.76 (2H, s, 2,6-aryl-H), 4.52 (2H, s, aryl-CH₂).

25 ii) Diphenylacetyl chloride (4.6g), tri-n-butyl-((3,5-bis(trifluoromethyl)phenyl)methoxymethyl)tin (12.6g; Example 1a, (Method Ai) and benzylchlorobis(triphenylphosphine) palladium (II) (80mg) were dissolved in chloroform (10ml) and the solution heated at 80°C for 6h. On cooling diethyl ether and saturated aqueous potassium fluoride were added and after 30 minutes the solution was filtered through HifloTM. The organic

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layer was washed with water, saturated brine and dried (MgSO_4). After evaporation in vacuo the residual oil was purified by chromatography on silica gel (eluting with 0 to 10% ethyl acetate in petroleum ether bp=60°-80°C) to give

5 1-(3,5-bis(trifluoromethyl)phenyl)methoxy-3,3-diphenyl acetone as an oil. ^1H NMR (CDCl_3 , 360MHz) δ 7.80 (1H; s; 4-aryl CH) 7.71 (2H; s; 2,6-aryl CH), 7.43-7.24 (10H; m; phenyl), 5.30 (1H; s; Ph_2CH), 4.56 (2H; s), 4.31 (2H; s). m/e Found 452.1191, $\text{C}_{24}\text{H}_{13}\text{F}_6\text{O}_2$ requires 452.12110.

Method B

i) To a solution of cyanohydrin (70% in water, 20ml) and powdered K_2CO_3 (90.7g) in ethyl acetate (250ml) was added 3,5-bis(trifluoromethyl)benzyl bromide (40.3g). the solution was

15 stirred at room temperature for 15 minutes then was heated to reflux for 2.5 hours. After cooling to room temperature water (500ml) and ethyl acetate (500ml) were added and the organic phase washed with saturated brine (2 times) and dried (MgSO_4). After removal of the solvent in vacuo the residual oil was

20 distilled under reduced pressure through a 3" vigreux column $b_p 1.8 = 92-108^\circ$ to give ((3,5-bis(trifluoromethyl)phenyl)methoxy)acetonitrile. ^1H NMR (250MHz, CDCl_3) δ 7.86 (1H, s), 7.82 (2H, s), 4.85 (2H, s), 4.40 (2H, s).

ii) To a cooled (-80°C) solution of

25 ((3,5-bis(trifluoromethyl)phenyl)methoxy)acetonitrile (0.51g; Example 1a, Method B(i) was added 0.42M lithio diphenylmethane (10ml; prepared by addition of 2.5M n-butyl lithium in hexane (10ml) to a cooled (-80°C) solution of diphenylmethane (4.2g) in diethyl ether (5ml), followed by

30 warming to room temperature for 3 hours). The solution was warmed to room temperature for 0.5h and then 1M-hydrochloric

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acid (10ml) and ethyl acetate were added and the organic phase washed with saturated brine and dried (MgSO_4). After evaporation in vacuo the residue was chromatographed on silica gel (eluting with 5% ethyl acetate in hexane) to give

5 1-(3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl acetone as an oil which gave an identical ^1H NMR spectrum to the material prepared by Method A.

b) 1-(3,5-Bis(trifluoromethyl)phenyl)methyloxy-3,3-diphenyl-2-hydroxypropane

10 To a solution of 1-(3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylacetone (Example 1a, 0.252g) in methanol (10ml) was added sodium borohydride (0.021g). After 0.5h the solution was evaporated to dryness and the residue was partitioned between ethyl acetate and 10% aqueous citric acid.

15 The organic phase was washed further with water, saturated brine and dried (MgSO_4). After evaporation in vacuo the residue was purified by silica gel chromatography (eluting with 20% ethyl acetate in hexane) to give 1-(3,5-bis

20 (trifluoromethyl)phenyl)methyloxy-3,3-diphenyl-2-hydroxypropane as an oil. ^1H NMR (360MHz, CDCl_3) δ 7.79 (1H; s; 4-aryl CH) 7.41-7.16 (10H; m; phenyl), 4.6 (1H; m; HOCH)

4.58 (2H; dd $J_{\text{gem}}=12.7\text{Hz}$; OCH_AH_B aryl), 4.10 (1H; d, $J=9.09\text{Hz}$; Ph_2CH), 3.57 (1H; dd $J=9.79\text{Hz}$, 2.93Hz ; $\text{CHCH}_A\text{H}_B\text{O}$), 3.45 (1H; dd, $J=9.76\text{Hz}$, 6.2Hz ; $\text{CHCH}_A\text{H}_B\text{O}$). Found: C, 63.05; H, 4.54; $\text{C}_{24}\text{H}_{22}\text{F}_6\text{O}_2$. 0.1(H_2O) requires C, 63.19; H, 4.46%.

25

EXAMPLE 2

1-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-((carboxamido)methyloxy)-3,3-diphenylpropane

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a) To a cooled solution (0°C) of 1-(3,5-bis(trifluoromethyl)phenyl)methyloxy-3,3-diphenyl-2-hydroxypropane (Example 1; 0.49g) in a mixture of tetrahydrofuran (4ml) and dimethylformamide (1ml) was added 80% sodium hydride (0.039g; suspension in oil). After 0.5 hours methyl bromoacetate (0.121ml) was added and the solution stirred at room temperature for 16 hours. Water (0ml) and ethyl acetate (50ml) were added and the organic phase washed with water (5 times), saturated brine and dried (MgSO₄). After removal of the solvent in vacuo the residue was purified by silica gel chromatography (eluting with 10% ethyl acetate in hexane) to give 1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-(carbomethoxy)methyloxy-3,3-diphenylpropane m/e CI⁺=544 (M+NH₄⁺).

b) To a cooled solution (0°C) of the product of Example 2a (0.2g) in methanol (20ml) was added ammonia gas until the solution was saturated. The flask was sealed to prevent escape of the ammonia and the solution stored at room temperature for 72 hours. The solution was then evaporated to dryness and the residue purified by chromatography on silica gel (eluting with 50% ethyl acetate in hexane) to give 1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-((carboxamido)methyloxy)-3,3-diphenylpropane as an oil, m/e Found 511.15840 C₂₆H₂₃F₆NO₃ requires 511.15821. ¹H NMR (360MHz, CDCl₃) δ 7.8 (1H; s; 4-aryl CH), 7.71 (2H; s; 2,6-aryl CH), 7.4-7.2 (10H; m; aryl), 6.0 (1H, bs; NH_AH_B), 5.7 (1H; bs; NH_AH_B), 4.53 (1H; d, Jgem=12.8Hz), 4.3 (1H; m; OCH-CH₂), 4.17 (1H; d J=9.4Hz; Ph₂CH), 4.03 (1H; d, Jgem=15.8Hz), 3.83 (1H; d, Jgem=15.8Hz) 3.6 (1H; dd, J=10.4 and 2.57Hz) 3.5 (1H; dd, J=10.4 and 5.52Hz)

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EXAMPLE 31-[3,5-Bis(trifluoromethyl)phenyl)methyl] 2-phenyl-2-ethane diol

- 5 a) (5)-(+)-Methyl mandelate (5.8h) and
3,4-dihydro-2H-pyran (3.3ml) were dissolved in dry
dichloromethane (40ml) containing pyridinium-p-toluene
sulphonate (0.84g). The mixture was stirred at room
temperature for 18 hrs. The reaction mixture was then washed
10 with water (50ml) and brine (50ml) and dried (MgSO_4).
Filtration and removal of solvent under reduced pressure gave
(5)-methyl-2-(tetrahydropyranyloxy)phenyl acetate as a clear oil
(6.4g) MS (CI^+) 251 ($\text{M}+\text{H}$) 268 ($\text{M}+\text{NH}_4$) (CI) 249 ($\text{M}-\text{H}$).
- 15 b) A solution of (5)-methyl-2-(tetrahydropyranyloxy)
phenyl acetate (6.4g) in dry tetrahydrofuran (10ml) was added
dropwise to a solution of lithium aluminium hydride (12.6ml,
1.0M) in dry tetrahydrofuran at 0°C . The reaction was allowed
to proceed for 1 hr and was then quenched by addition of 4N
sodium hydroxide solution. The mixture was filtered and the
20 filtrate extracted into ethyl acetate, dried (MgSO_4), filtered and
the solvent removed under reduced pressure to afford a clear oil.
The recovered oil was dissolved in dry dimethylformamide (20ml)
and treated with sodium hydride (0.8g, 60%). The mixture was
stirred at room temperature for 25mins and then treated with
25 3,5-bis(trifluoromethyl)benzyl bromide (3.6ml). The reaction was
allowed to stir at room temperature for 18 hrs, quenched by the
addition of water (200ml), and extracted into ethyl acetate
(100ml). The organic layer was evaporated, and washed with
water (200ml), brine (100ml), dried (MgSO_4), filtered and the
30 solvent removed under reduced pressure to give a yellow oil.
Purified by flash chromatography on silica gel (EtOAc/nHex)

- 30 -

1:19) afforded a clear oil (4.0g) which was dissolved in a solution of 10% 3NHCl in methanol (20ml). The reaction was stirred at room temperature for 1 hr at which time no starting material would be detected. Solvent was removed and reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was separated dried (MgSO_4), filtered and the solvent removed under reduced pressure to afford the product as a clear oil. ^1H NMR (360MHz, CDCl_3) δ 3.63 (1H, dd, $J=8.5$ and 1.0 Hz), 3.71 (1H, dd, $J=3.5$ and 1.0 Hz), 4.64 (2H, s), 5.0 (1H, dd, $J=3.5$ and 1.0 Hz), 7.22-7.40 (5H, m), 7.78 (2H, s), 7.84 (1H, s). MS (CI^+) 382 [$\text{M}+\text{NH}_4$]; $\text{C}_{17}\text{H}_{14}\text{O}_2\text{F}_6$ requires C, 56.65; H, 3.87. Found C, 55.86; H, 3.91%

EXAMPLE 4

1-[(3,5-bis(trifluoromethyl)phenyl)methyl] 2-phenyl-2-[N-methyl-N(3-pyridylmethyl)acetamido ethane diol hydrochloride salt

Sodium hydride (110mg, 60%) was added to a stirred suspension of the compound of Example 3 (500mg) and 3-N-methyl(chloroacetamidomethyl)pyridine hydrochloride (320mg) in dry dimethylformamide (8.0ml). The mixture was warmed to 60°C for 2 hrs, then cooled to room temperature and poured into water (100ml), and extracted into ethyl acetate. The organic layers were separated and washed with water (100ml), brine (50ml), dried (MgSO_4), filtered and the solvent removed under reduced pressure to afford a brown oil. Purified by flash chromatography on silica gel (EtOAc). The purified product was dissolved in dry ether (10ml) and treated with a saturated solution of HCl in ether to give a white precipitate. Recrystallisation from ether gave the product as white needles. mp. 123°C. ^1H NMR (360MHz, DMSO) δ 2.8 (1H, s), 2.95 (3H, s),

- 31 -

3.60-3.84 (2H, m), 4.23 (2H, q, J=7.0 Hz), 4.64 (2H, s), 4.72 (2H, s), 7.14-7.21 (4H, m), 7.84 (1H, s), 7.90 (2H, s), 7.92 (1H, s), 8.04 (1H, m), 8.41 (1H, m), 8.82 (2H, m). $C_{26}H_{24}F_6N_2O_3 \cdot HCl \cdot 0.25H_2O$ requires C, 55.03; H, 4.53; N, 4.94. Found C, 55.05; H, 4.52; N, 4.79%.

EXAMPLE 5

10 Methyl-2-hydroxy-[1-phenyl-2-((3,5-bis(trifluoromethyl)phenyl)methyloxymethyl)acetate

Sodium hydride (25mg, 60%) was added to a stirred solution of methylbromoacetate (84mg) and 1-[3,5-bis(trifluoromethyl)benzyl]-2-phenyl-2-ethanediol (200mg) in dry dimethylformamide (0.5ml). The mixture was stirred at 23°C for 15 18 hrs, then partitioned between water and ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with 9:1 hexanes:ethyl acetate to give the title compound as a clear oil. 1H NMR (250MHz, $CDCl_3$) δ 3.60-3.68 (1H, m), 3.68 (3H, s), 3.80-3.94 (1H, m), 3.95-4.21 (2H, q), 4.64-4.80 (3H, m), 7.23-7.39 (5H, m), 7.80 (3H, s).

EXAMPLE 6

25 Methyl-2-hydroxy-[2-phenyl-2-((3,5-bis(trifluoromethyl)phenyl)methyloxymethyl)acetamide

Anhydrous methylamine gas was bubbled through a solution of methyl-2-hydroxy-[1-phenyl-2-(3,5-bis(trifluoromethyl)benzyloxymethyl) acetate (200mg) for 10 30 minutes. The solution was then transferred to a thick-walled

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sealed flask and stored at 4°C for 18 hrs. The mixture was cooled to -78°C before opening, then concentrated *in vacuo*. Residue was purified by flash column chromatography on silica gel eluting with 1:1, hexanes:ethyl acetate to give the title compound as a clear oil. ¹H NMR (360MHz, CDCl₃) δ 2.71 (3H, d, J = 4.9Hz), 3.63-3.66 (1H, dd, J = 3.1Hz), 3.75-3.83 (2H, m), 4.01-4.05 (1H, d, 16Hz), 4.53-4.59 (1H, dd, J = 3.0Hz), 4.70 (2H, s), 7-7.72 (1H, b), 7.31-7.40 (5H, m), 7.81 (2H, s), 7.84 (1H, s). MS (CI⁺) 436 [M], 453 [M+NH₄]. C₂₀H₁₉F₆NO₃ requires C, 55.18; H, 4.40; N, 3.22. Found C, 55.27; H, 4.47; N, 3.11.

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The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 7A Tablets containing 1-25mg of compound

| | | | | |
|----|----------------------------|------------------|------|------|
| 5 | | <u>Amount mg</u> | | |
| | Compound of formula (I) | 1.0 | 2.0 | 25.0 |
| | Microcrystalline cellulose | 20.0 | 20.0 | 20.0 |
| | Modified food corn starch | 20.0 | 20.0 | 20.0 |
| | Lactose | 58.5 | 57.5 | 34.5 |
| 10 | Magnesium Stearate | 0.5 | 0.5 | 0.5 |

EXAMPLE 7B Tablets containing 26-100mg of compound

| | | | | |
|----|---|------------------|-------|-------|
| | | <u>Amount mg</u> | | |
| | Compound of formula (I) | 26.0 | 50.0 | 100.0 |
| 15 | Microcrystalline cellulose | 80.0 | 80.0 | 80.0 |
| | Modified food corn starch | 80.0 | 80.0 | 80.0 |
| | Lactose | 213.5 | 189.5 | 139.5 |
| | Magnesium Stearate | 0.5 | 0.5 | 0.5 |
| 20 | The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing | | | |
| 25 | 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet. | | | |

EXAMPLE 8 Parenteral injection

| | | |
|----|-------------------------|------------------|
| | | <u>Amount mg</u> |
| 30 | Compound of formula (I) | 1 to 100mg |
| | Citric Acid Monohydrate | 0.75mg |
| | Sodium Phosphate | 4.5mg |
| | Sodium Chloride | 9mg |
| | Water for Injections | to 1ml |

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The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

5

EXAMPLE 9 Topical formulation

| | <u>Amount mg</u> |
|-------------------------|------------------|
| Compound of formula (I) | 1-10g |
| Emulsifying Wax | 30g |
| 10 Liquid paraffin | 20g |
| White Soft Paraffin | to 100g |

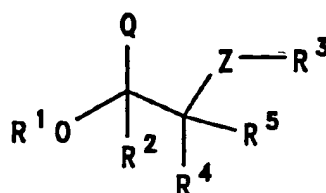
The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

15

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CLAIMS

1. A compound of formula (I), or a salt or
5 prodrug thereof:



(I)

wherein

- 15 Q represents optionally substituted phenyl or optionally substituted benzhydryl;

R¹ represents: H;

- C₁₋₆alkyl optionally substituted by hydroxy, cyano, COR^a, COOR^a, CONR^aR^b, COC₁₋₆alkylNR^aR^b,
20 CONR¹²C₁₋₆alkylOR^a; Het; COHet; CONR¹²C₁₋₆alkylHet;
CONR¹²C₁₋₆alkylCONR^aR^b or NR^aR^b;

phenyl(C₁₋₄alkyl) (optionally substituted by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl in the phenyl ring);

- 25 C₂₋₆alkenyl;

C₂₋₆alkynyl;

COR^a;

COOR^a;

COHet;

- 30 COC₁₋₆alkylhalo;

COC₁₋₆alkylNR^aR^b;

CONR¹²C₁₋₆alkylCONR^aR^b;

CONR^aR^b; or

SO₂R^a;

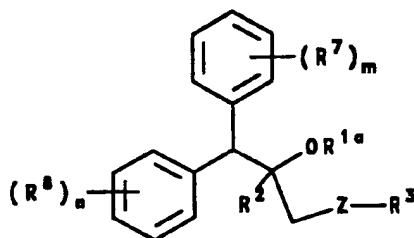
- 36 -

- R^2 represents H, C_{1-6} alkyl or C_{2-6} alkenyl;
or R^1 and R^2 together form a chain $(CH_2)_q$
optionally substituted by oxo where q is 4 or 5 and where
one methylene group may optionally be replaced by an
5 oxygen atom or a group NR^X , where R^X is H or C_{1-6} alkyl;
 R^3 represents C_{1-3} alkyl substituted by a phenyl
group which may itself optionally be substituted by one
or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo,
cyano, nitro, trifluoromethyl, trimethylsilyl, SR^C , SOR^C ,
10 SO_2R^C , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ and $CONR^C R^d$;
 R^4 and R^5 each represent H, C_{1-6} alkyl or
 C_{2-6} alkenyl;
 Z represents O or S;
 R^{12} represents H, C_{1-6} alkyl, phenyl (optionally
15 substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo
and trifluoromethyl) or phenyl(C_{1-4} alkyl) (optionally
substituted in the phenyl ring by one or more of
 C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl);
 R^a and R^b each independently represent H, C_{1-6}
20 alkyl, phenyl (optionally substituted by one or more of
 C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl),
phenyl(C_{1-4} alkyl) (optionally substituted in the phenyl
ring by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and
trifluoromethyl) or R^a and R^b together form a chain
25 $(CH_2)_p$ optionally substituted by oxo where p is 4 or 5
and where one methylene group may optionally be replaced
by an oxygen atom or a group NR^X , where R^X is H or C_{1-6}
alkyl;
 R^C and R^d independently represent H, C_{1-6} alkyl,
30 phenyl or trifluoromethyl; and
Het represents an aromatic heterocycle
optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, oxo,
thioxo, halo, trifluoromethyl, $NR^a R^b$, $NR^a COR^b$, $CONR^a R^b$,

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CO_2R^a , SR^a , SO_2R^a or CH_2OR^a , where R^a and R^b are as above defined.

2. A compound as claimed in claim 1 of
5 formula (IA):



(IA)

15 wherein

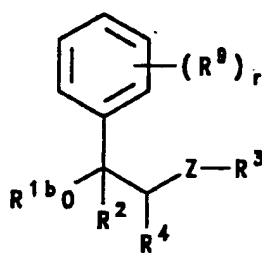
Z , R^2 and R^3 are as defined for formula (I) above;

R^{1a} represents H or C_{1-6} alkyl optionally substituted by hydroxy, cyano, COR^a , COOR^a , CONR^aR^b ,
20 $\text{COC}_{1-6}\text{alkylNR}^a\text{R}^b$, $\text{CONR}^{12}\text{C}_{1-6}\text{alkylOR}^a$,
 $\text{CONR}^{12}\text{C}_{1-6}\text{alkylCONR}^a\text{R}^b$ or NR^aR^b (where R^a , R^b and R^{12} are as defined for formula (I) above); phenyl(C_{1-4} alkyl) (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl in the phenyl ring);
25 C_{2-6} alkenyl; C_{2-6} alkynyl; COR^a ; COOR^a ; $\text{COC}_{1-6}\text{alkylhalo}$; $\text{COC}_{1-6}\text{alkylNR}^a\text{R}^b$; $\text{CONR}^{12}\text{C}_{1-6}\text{alkylCONR}^a\text{R}^b$; CONR^aR^b ; or SO_2R^a ; or R^1 and R^2 together form a chain $(\text{CH}_2)_q$ optionally substituted by oxo where q is 4 or 5 and where one methylene group may optionally be replaced by an
30 oxygen atom or a group NR^x , where R^x is H or C_{1-6} alkyl;
each R^7 independently represents C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl;
each R^8 independently represents C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl; and

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n and m each represent 0, 1, 2 or 3; or a salt or prodrug thereof.

3. A compound as claimed in claim 1 of
5 formula (IB):



(IB)

15 wherein Z, R^3 and R^4 are as defined for formula (I) above;

R^{1b} represents: H;

C_{1-6} alkyl optionally substituted by hydroxy, cyano, COR^a , $COOR^a$, $CONR^aR^b$, $COC_{1-6}alkylNR^aR^b$,
20 $CONR^{12}C_{1-6}alkylOR^a$, Het; COHet; $CONR^{12}C_{1-6}alkylCONR^aR^b$ or NR^aR^b ;

phenyl(C_{1-4} alkyl) (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl in the phenyl ring);

25 C_{2-6} alkenyl;

C_{2-6} alkynyl;

COR^a ;

$COOR^a$;

COHet;

30 $COC_{1-6}alkylhalo$;

$COC_{1-6}alkylNR^aR^b$;

$CONR^{12}C_{1-6}alkylCONR^aR^b$;

$CONR^aR^b$; or

SO_2R^a ;

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where R^a , R^b and R^{12} are as defined for formula (I) above;

R^2 represents H, C_{1-6} alkyl or C_{2-6} alkenyl;

each R^9 independently represents C_{1-6} alkyl,

5 C_{1-6} alkoxy, halo or trifluoromethyl;

r represents 0, 1, 2 or 3; and

Het represents an aromatic heterocycle

optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, oxo,

thioxo, halo, trifluoromethyl, NR^aR^b , NR^aCOR^b , $CONR^aR^b$,

10 CO_2R^a , SR^a , SO_2R^a or CH_2OR^a , where R^a and R^b are as above defined; or a salt or prodrug thereof.

4. A compound as claimed in claim 1 wherein Q is optionally substituted benzhydryl.

15

5. A compound as claimed in claim 1 wherein Q is optionally substituted phenyl.

6. A compound as claimed in claim 1, claim 4 or claim 5 wherein R^1 represents H or C_{1-4} alkyl substituted by $CONR^aR^b$, $COOR^a$ or $CONR^{12}C_{1-6}$ alkylHet.

20

7. A compound as claimed in any preceding claim wherein R^3 represents C_{1-3} alkyl substituted by a phenyl group, which phenyl group is substituted by one or two substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl and halo.

25

8. A compound as claimed in any preceding claim wherein Z is O.

30

9. A compound as claimed in claim 1 selected from:

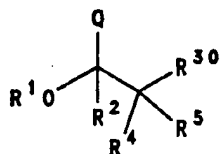
- 40 -

- 1-(3,5-bis(trifluoromethyl)phenyl)methyloxy-3,3-diphenyl-2-hydroxypropane;
 1-(3,5-bis(trifluoromethyl)phenyl)methyloxy-2-((carboxamido-methyloxy)-3,3-diphenylpropane;
 5 1-[(3,5-bis(trifluoromethyl)phenyl)methyl]-2-phenyl-2-ethane diol;
 1-[(3,5-bis(trifluoromethyl)phenyl)methyl]-2-phenyl-2-[N-methyl-N(3-pyridylmethyl)acetamido ethane diol;
 methyl-2-hydroxy-[1-phenyl-2-((3,5-bis(trifluoromethyl)phenyl)methyloxymethyl)]acetate;
 10 methyl-2-hydroxy-[1-phenyl-2-((3,5-bis(trifluoromethyl)phenyl)methyloxymethyl)]acetamide;
 and salts and prodrugs thereof.

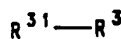
15 10. A compound as claimed in any preceding claim for use in therapy.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9 in
 20 association with a pharmaceutically acceptable carrier.

12. A process for the preparation of a compound as claimed in claim 1, which process comprises:
 (A) reacting a compound of formula (II) with a
 25 compound of formula (III):



(II)

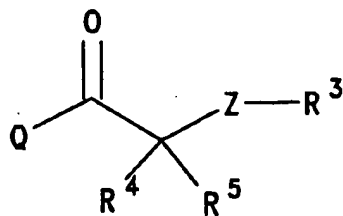


(III)

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wherein Q, R², R³, R⁴ and R⁵ are as defined for formula (I), R¹ is as defined for formula (I) **except that**, when R¹ is H it is replaced by a suitable protecting group, such as tetrahydropyranyl; and one of R³⁰ and R³¹ represents a leaving group and the other of R³⁰ and R³¹ represents ZH, where Z is as defined for formula (I); in the presence of a base, followed by deprotection, if required; or

(B) reduction of a compound of formula (IV):



(IV)

wherein Q, R³, R⁴, R⁵ and Z are as defined for formula (I); and optionally converting the compound of formula (I) so obtained to another compound of formula (I) or a salt or prodrug.

13. A method for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin-reducing amount of a compound according to claim 1.

14. A method according to claim 13 for the treatment or prevention of pain or inflammation.

15. A method according to claim 13 for the treatment or prevention of migraine.

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16. A method according to claim 13 for the treatment or prevention of arthritis.

5 17. The use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

10 18. The use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for the treatment of pain or inflammation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 93/01863

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07C235/06 C07C43/178 C07D213/40 C07C69/708 A61K31/16
A61K31/44 A61K31/085

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | TETRAHEDRON LETTERS. vol. 24, no. 31, 1983, OXFORD GB pages 3163 - 4 E.J. COREY ET. AL. 'A new and simple synthesis of alkoxy and aryloxymethyl lithium reagents' see table 1 | 1-3,5,7, 8,12 |
| X | SYNLETT no. 5, May 1992, STUTTGART DE pages 415 - 6 T. AKIYAMA ET. AL. 'Trimethylsilyl chloride- Tin(II)chloride-Anisole. A novel selective p-methoxybenzyl ether cleavage reagent' see table 1, entry no. 9 | 1-3,5,7, 8,12 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- 'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'&' document member of the same patent family

Date of the actual completion of the international search

25 November 1993

Date of mailing of the international search report

- 7. 12. 93

Name and mailing address of the ISA

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Fax (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/01863

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | GB,A,1 448 437 (BEECHAM) 8 September 1976 cited in the application see claims; examples --- | 1-12 |
| A | US,A,3 960 960 (HÖLLINGER ET. AL.) 1 June 1976 cited in the application see claims; examples --- | 1-12 |
| A | EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO.) 31 October 1990 cited in the application see claims; examples --- | 1-18 |
| A | EP,A,0 436 334 (PFIZER) 10 July 1991 cited in the application see claims; examples ----- | 1-18 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/01863

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13-16 are drawn to a method of treatment of the human or animal body by therapy, the search has been carried out and based on the alleged effect of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The claims are so broadly formulated that a complete search is not possible within a reasonable time limit. The search has been limited to prepared examples (see Guidelines, B. Chapt. III, 3.7).
Claims searched incompletely: 1-18
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 93/01863

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| GB-A-1448437 | 08-09-76 | NONE | |
| US-A-3960960 | 01-06-76 | AT-A- 319916 | 10-01-75 |
| | | AU-A- 6018473 | 13-03-75 |
| | | BE-A- 804692 | 11-03-74 |
| | | BE-A- 536091 | |
| | | CA-A- 986138 | 23-03-76 |
| | | CH-A- 590206 | 29-07-77 |
| | | CH-A- 596144 | 28-02-78 |
| | | DE-A, B, C 2339528 | 18-04-74 |
| | | FR-A, B 2198740 | 05-04-74 |
| | | FR-A- 1102498 | |
| | | GB-A- 1377350 | 11-12-74 |
| | | GB-A- 804692 | |
| | | JP-C- 938957 | 30-01-79 |
| | | JP-A- 49062452 | 17-06-74 |
| | | JP-B- 53020033 | 24-06-78 |
| | | LU-A- 68308 | 23-11-73 |
| | | NL-A- 7312515 | 13-03-74 |
| | | SE-B- 413892 | 30-06-80 |
| | | US-A- 2838510 | |
| | | US-A- 2838590 | |
| EP-A-0394989 | 31-10-90 | JP-A- 3027399 | 05-02-91 |
| | | US-A- 5164372 | 17-11-92 |
| EP-A-0436334 | 10-07-91 | WO-A- 9109844 | 11-07-91 |
| | | EP-A- 0558156 | 01-09-93 |